by Timothy M. O’Brien and Troy A. Rafferty

The Bisphosphonate Irony:
Fosamax-Induced Femur Fractures

Osteoporosis is a disease affecting millions of postmenopausal women. Osteoporosis causes fractures. "Bisphosphonate" osteoporosis medications like Fosamax are prescribed to prevent fractures. Ironically, the osteoporosis medications like Fosamax that are supposed to prevent fractures actually are causing horrific fractures of women's femurs, usually resulting in highly invasive surgical fixes such as open reduction/internal fixation of the femur.

For approximately five years, product liability cases have been pending against Merck’s osteoporosis drug, Fosamax, involving Fosamax's now well accepted propensity to cause a disease appropriately named “bisphosphonate-related osteonecrosis of the jaw.” Unfortunately, despite having one of the highest side effect profiles of any drug in the U.S. prescription database, Fosamax remains on the market, and available by prescription. More recently, it has been disclosed that Fosamax not only causes bisphosphonate-related osteonecrosis of the jaw but also can cause the largest bone in a woman's body – the femur (thigh) – to snap without any trauma precipitating the fracture. Because Fosamax is designed to, and very effectively halts, normal biologic bony processes, women who take Fosamax long-term are at risk of developing dense but precariously fragile bones which can fracture without trauma and without warning.
The reason why Fosamax can harm human bones is that Fosamax, by its express design, is targeted to directly oversuppress a naturally occurring process in the human bones: bone turnover. The body relies on bone turnover to keep bones resilient.

I. The Same Biologic Process Which Causes Bisphosphonate-Related Osteonecrosis Of The Jaw Causes Fosamax-Induced Femur Fractures.

Fosamax is a bisphosphonate (or as some articles call it, diphosphonate). There are two classes of bisphosphonates: the N-containing (nitrogenous) and non-N-containing (non-nitrogenous) bisphosphonates. The nitrogenous bisphosphonates include the following: pamidronate (Aredia); ibandronate (Boniva); risedronate (Actonel); zoledronate (Zometa); and alendronate (Fosamax). The non-nitrogenous bisphosphonates include the following: etidronate (Didronel); clodronate (Bonefos and Loron); and tiludronate (Skelid). The presence of the nitrogen atom in the Fosamax formulation is critical to understanding the dangers of Fosamax and the long-range risks that Fosamax use presents.

For years, physicians and dentists in the oncologic and dental communities have acknowledged the observed risk of osteonecrosis of the jaw (ONJ) caused by bisphosphonate drugs, including Fosamax. Additionally, in August 2004, the United States Food & Drug Administration Office of Drug Safety (“ODS”) issued a report based upon its review of post-marketing reports of Fosamax-associated ONJ. The ODS found the risk of ONJ to be a class effect common to the nitrogenous bisphosphonates, including Fosamax. The FDA observed that the risk of ONJ extended to the oral bisphosphonates, chiefly Merck’s Fosamax, and that Merck should proactively advise prescribers and patients of the risk.

More recent developments in the medical literature demonstrate that the dangers of Fosamax extend well beyond the bones in the jaw and into the very bone that allow us to stand upright and walk the femur. The reason why Fosamax can harm human bones is that Fosamax, by its express design, is targeted to directly oversuppress a naturally occurring process in the human bones: bone turnover. The body relies on bone turnover to keep bones resilient.

In this regard, it is important to understand the relationship between osteoclasts and osteoblasts and their function in maintaining healthy bones. The bones in the body are constantly purged and remodeled by bone cells known as the osteoclasts and osteoblasts. Osteoclasts are the garbage men of the bone construction industry. They remove tired, dead, infected, or compromised bone tissue and dispose of it. Osteoblasts are the construction workers. When the old bone tissue is removed by osteoclasts, new healthy bone is built in its stead by osteoblasts. This process is known as bone turnover.

The process by which Fosamax works to prevent osteoporosis is through the inhibition of osteoclasts; by inhibiting osteoclasts, bisphosphonates inhibit bone material from being resorbed (or removed) by osteoclasts. “However, normal osteoclasts are vital to bone turnover and bone viability. ... Interruption of this homeostatic cycle by overly effective inhibition of bone resorption results in the accumulation of nonvital osteocytes and micro fractures of the old mineral matrix.” Just as this process compromises the ability of the human jaw bones to heal, fight infection, and renew themselves, it also directly impacts the ability of the long bones, including the femur, to retain the necessary plasticity to flex and meet the everyday demands of walking and standing. According to an internal FDA statistical review of Merck’s biopsy data pertaining to Fosamax, Fosamax suppresses the naturally occurring bone turnover by 94 percent. If the patient is also on hormone replacement therapy, the resulting suppression is 98 percent to 100 percent.

The presence of nitrogen in alendronate is critical to understanding the accumulation of Fosamax and the greater propensity for adverse effects the longer the patient is on the drug. The nitrogen atom’s ability to stop the metabolism and clearance from the bone tissue of bisphosphonate chemicals results in an ever-increasing bisphosphonate toxicity as the patient continues to ingest Fosamax tablets: “The nitrogen side chain prevents these drugs from being metabolized, allowing them to accumulate with ongoing effects.”

As a result of the presence of the nitrogen atom, Fosamax has a half-life in the bone of more than ten years. As patients take dose after dose of Fosamax, this incredibly long half-life results in a massive cumulative dose over the multi-year dosing cycle.

Just as marked inhibition of bone remodeling which occurs with Fosamax use predisposes patients to osteonecrosis in the jaw bones, years of oversuppressed bone turnover predispose Fosamax patients to horrific fractures of the femur with no inciting trauma; the fracture typically occurs immediately below the trochanter (head) of the femur. Thus, the fractures are referred to as low-energy subtrochanteric femur fractures. A recent study from Cornell University’s Hospital for Special Surgery revealed that Fosamax patients were 139 times (i.e., 13,900 percent) more likely to suffer from these non-traumatic fully displaced fractures of the subtrochanteric femur than were patients not on Fosamax. The Cornell researchers saw no such fractures in osteoporotic patients who were not being treated with Fosamax.
II. Fosamax-Induced Femur Fractures Are Painful And Life-Changing.

By overmarketing the ability of Fosamax to prevent fractures for all post-menopausal women, Merck successfully moved Fosamax from a “niche” market of $200 million per year into a multi-billion dollar blockbuster drug. Before its patent exclusivity ended in 2008, Fosamax was one of Merck’s biggest sellers, approximating $3.5 billion per year in sales. Merck grew this product to its record-setting pace by overstating the benefits of the drugs and minimizing risks of Fosamax.

The FDA sent numerous warning letters to Merck, admonishing it to refrain from overstating the benefits of Fosamax and for minimizing the risks. No less than five letters from the FDA’s Division of Drug Marketing, Advertising, and Communications (“DDMAC”) were sent to Merck on the following dates December 15, 1995; April 14, 1997; July 2, 1997; July 16, 1999; and June 20, 2001.

Consistent with Merck’s overstatement of the Fosamax-conferring benefits, and minimization of Fosamax-conferring risks, published medical literature reveals that the actual benefit conferred by Fosamax in the treatment of actual patients is significantly less than that which is propounded by the Merck-sponsored clinical trials testing the efficacy of the drug. “The incident of fractures during treatment with antiresorptive agents in a clinical setting is considerably higher than that observed in randomized clinical trials.” Additionally, studies demonstrate that over-the-counter Vitamin D and Calcium supplements demonstrate a stunningly similar fracture reduction profile to that of Fosamax.

Merck’s marketing of Fosamax was directed to a “Fosamax for Life” program, inferring that once women were on Fosamax, they were to continue taking the drug for the remainder of their lives. However, this is problematic for two reasons. First is the long ten-year half-life and the accumulation of the dosage in the bones. Second, data contained in the medical literature reveals that the marginal benefit conferred by Fosamax diminishes over time as bones become more brittle due to the Fosamax use. Medical literature shows that long-term Fosamax use reduces the bones’ vitality and ability to withstand fracture. Further, recent medical literature demonstrates that Fosamax patients can be taken completely off of Fosamax for up to five years, and the fracture rate will not increase during that “drug holiday” – presumably due to the long half-life of the drug. However, nowhere in Merck’s prescriber information is there any information about the ability of prescribers to give “drug holidays” in order to decrease their patients’ exposure periods and risk of side effects.

This is the type of information which was not conveyed to patients taking the drug nor to the doctors who prescribed the drug.

Further, again, an unpublished FDA statistical analysis of Merck’s pivotal clinical trial data shows that Fosamax only prevents fractures for a very short period of time. When reviewing 54 months of Merck’s pivotal clinical trial, the FDA statistical reviewer concluded: “Fosamax provides no advantage over Placebo in either the first 18 months or the last 18 months [but] Fosamax does provide protection against fracture in the middle 18 months.”

As patients get beyond the utility period of Fosamax, and prescribers keep them on the drug, they achieve absolutely no fracture reduction and, ironically, assume the horrific risks of osteonecrosis of the jaw, subtrochanteric femur fractures and now, it appears, esophageal cancer. Before late last year, a prescribing physician reviewing the Fosamax label would find no information about the limited duration of Fosamax’s fracture reduction efficacy and absolutely no warning or precaution about the ability of Fosamax to actually cause fractures of the very bone it purports to protect.

Fosamax-induced femur fractures typically occur just below the trochanter, although numerous cases are also occurring at the mid-shaft. The typical scenario involves bone which is not porous, is dense, but “hypermineralized” and thus brittle. The fracture typically is fully displaced with “beaking” (the displaced portions of bones resemble bird beaks or mountain tops) of the cortex. The treatment of these fractures is almost universally “open reduction/internal fixation” of the femur with screws and intramedullary rods. Very frequently, these fractures will occur bilaterally. For those patients who have “only” one femur fracture, orthopedic surgeons frequently advise the patient that the x-ray films reveal that the other femur is at high risk for fracture due to its Fosamax-induced hypermineralization which results in microcracks along the shaft of the bone.
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For a healthy, young patient, an open reduction internal fixation of the femur is a horrific surgery and rehabilitation process to endure. For a seventy year old Fosamax patient, who has taken thousands upon thousands of dollars worth of Fosamax pills, it is life-threatening. For such a patient, the in-patient rehabilitation course can consume several weeks if not months.

III. Emerging Developments Regarding Fosamax-Induced Femur Fractures.

The first Fosamax-induced femur fracture lawsuit was filed in January 2008. Since that time, hundreds of similar cases have been filed in the Superior Court of Atlantic County, New Jersey, where they are consolidated before the Honorable Carol Higbee. At the time the original suit was filed, there was no warning relating to the risk of femur fractures from Fosamax use.

In the Spring of 2010, however, ABC News’ Diane Sawyer covered the Fosamax-induced femur fracture problem as the lead story for several nights on ABC News’ World News Tonight. Shortly after that, the American Society of Bone & Mineral Research, an organization funded largely by osteoporosis medication giants such as Merck, Eli Lilly, and Roche, convened a Task Force to look into the problem of the adynamic bone and low energy femur fractures associated with bisphosphonate use. The Task Force strongly recommended that bisphosphonate medications contain warnings about the risk of femur fractures from prolonged bisphosphonate use. Subsequently, bisphosphonate manufacturers, including Merck, began warning of the risk of low energy femur fractures from prolonged bisphosphonate use.

Conclusion

While the new warning certainly is welcome, it does not eradicate Merck’s liability for failure to warn – particularly since it is too little and too late. Most of the patients who are going to suffer from these adynamic bone fractures have been on Fosamax for years before the first warning was ever included by Merck in its Fosamax label. Further, for states which follow §402A of the Restatement of Torts Second, Products Liability, the utility/risk-benefit analysis shows that this product is a defeasibly designed product as the patient’s risk skyrockets at the same time as the fracture reduction efficacy of the drug plummet. The risk is there, the benefit is not there, particularly after three years of use. Far from its glory days of nearly $4 billion in annual sales, Fosamax is now a ghost of its former self. But the Fosamax blockbuster legacy lives on as thousands of American women suffer needlessly from the fractures caused by the drug which was supposed to protect them from fracture.

1 Fosamax is the trade name for the chemical compound alendronate sodium.
2 United States Food & Drug Administration, Office of Drug Safety, Division of Drug Risk Evaluation, ODS Postmarketing Safety Review, ODS P ID# D040283, 08/25/04 (hereinafter “FDA Rvw.”)
8 Farrugia, p. 115.
12 Nevisar, p. 348.
14 Bess Dawson Hughes, et al., Effect of Calcium and Vitamin D Supplementation on Bone Density in Men and Women 65 Years of Age or Older. NEJM 337: 670-6, 1997.
19 Nevisar, p. 346.
20 Tesoriero, HW, Fight Brews Over Merck Product, WALL STREET JOURNAL 01/30/08, p A12.

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